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(54) Title: METHOD FOR TREATING A LACTIC RAW MATERIAL CONTAINING GMP

(54) Titre: PROCEDE DE TRAITEMENT D'UNE MATIERE PREMIERE LACTIQUE CONTENANT DU GMP

(57) Abstract

The invention concerns a simple ion-exchanging industrial process which consists in treating a liquid lactic raw material containing glycomacropeptide in the presence of a weak anionic resin to obtain an improved protein product useful in food processing and said glycomacropeptide which is selectively adsorbed on the resin, then eluted in said resin. Before being treated with resin, the liquid raw material is decationized so that its pH has a value between 1 and 4.5.

(57) Abrégé

Un procédé industriel simple d'échange d'ions consiste à traiter une matière première lactique liquide contenant le glycomacropeptide en présence d'une résine anionique faible de manière à obtenir un produit protéique amélioré utilisable en alimentation et ledit glycomacropeptide qui est adsorbé sélectivement sur la résine, puis élué de ladite résine. Avant le traitement avec la résine, la matière première liquide est décationisée de sorte que le pH ait une valeur de 1 à 4,5.

Abstract

Process for the treatment of a lactic raw material

A simple industrial ion-exchange process consists in treating a liquid lactic raw material containing glycomacropeptide in the presence of a weak anionic resin so as to obtain an improved protein product which can be used in foods and the said glycomacropeptide which is selectively adsorbed onto the resin, and then eluted from the said resin.
Figure 1.

Process for the treatment of a lactic raw material

The invention relates to a process for the treatment of a lactic raw material containing glycomacropeptide or caseinoglycomacropeptide (hereinafter GMP), with the aim of separating the said GMP therefrom.

GMP is a phosphorylated and partially sialylated macropeptide which is formed by the action of a protease, for example rennet, on mammalian milk kappa-casein. It represents about 20% by weight of the proteins in the sweet whey obtained after separation of casein during cheese manufacture.

A process for the manufacture of GMP at the laboratory level is known which consists in treating a raw material of lactic origin, such as for example an acid casein or a caseinate, which are hydrolysed by rennet, or alternatively a demineralized and lactose-free sweet whey from cheesemaking, with trichloroacetic acid so as to precipitate the proteins, and then in recovering the supernatant, in dialysing it and finally in drying the dialysate. Such a process is not industrial.

A process for the production of GMP on an industrial scale, which is described in EP-A-0,488,589, consists in treating a whey product by ion exchange, in recovering the fraction that has not been adsorbed, in concentrating it and in demineralizing it by ultrafiltration, diafiltration and, where appropriate, reverse osmosis and in recovering the GMP.

A process for the production of a whey protein fraction is described in UK-A-2,188,526. It consists in treating a milk product with a strong anionic resin, under conditions such that the proteins and some peptides of the treated material are nonselectively adsorbed onto the resin in the form of complexes. Such complexes are difficult to subsequently elute from the resin. The

eluate is characterized by the formation of a firm gel at a pH of less than 4.5 and at room temperature once it is suspended in water. The protein fraction may be used in drinks of the milk-shake type and in dessert mousses.

In JP-A-07132049, it is proposed to use a weakly anionic ion exchange resin whose matrix is hydrophilic to separate the sialylated peptides from whey. The method used consists in passing the raw material, whose pH has been precisely adjusted beforehand to a value of 4 to 6, over a hydrophilic macromolecular support consisting of a natural polysaccharide or a synthetic polyvinyl, grafted with basic exchanging groups. The supports used as matrix are not easily applicable industrially.

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

It is an object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative.

The invention therefore relates to a process for the ion-exchange treatment of a liquid lactic raw material containing GMP, with the aim of recovering, on the one hand, a product which can be used directly as protein source and, on the other hand, GMP in purified form, comprising the following steps:

i) decationization of the liquid raw material, such that the pH has a value of 1 to 4.5,

ii) bringing the said liquid into contact with a weak anionic resin of hydrophobic matrix, predominantly in alkaline form up to a stabilized pH,

iii) separation of the resin and the liquid product which is recovered, and

iv) desorption of GMP from the resin.

As lactic raw material, there may be used in the process according to the invention any product or by-

product containing GMP. There may be mentioned as a guide:

- sweet whey obtained after separation of casein coagulated with rennet,
- a sweet whey or such a whey demineralized to a greater or lesser degree, for example by electrodialysis, ion exchange, reverse osmosis, electrodeionization or a combination of these procedures,
- a concentrate of sweet whey,
- a concentrate of sweet whey demineralized to a greater or lesser degree, for example by electrodialysis, ion exchange, reverse osmosis, electrodeionization or a combination of these procedures,
- a concentrate of proteins of substantially lactose-free sweet whey obtained, for example, by ultrafiltration, followed by diafiltration (ultrafiltration with washing),
- mother liquors of the crystallization of lactose from a sweet whey,
- a permeate of ultrafiltration of a sweet whey,
- the product of hydrolysis, by a protease, of a native casein obtained by acid precipitation of skimmed milk with an inorganic acid or by biological acidification, where appropriate with addition of calcium ions or alternatively of a micellar casein, obtained for example by microfiltration of a skimmed milk,
- the product of hydrolysis of a caseinate by a protease.

A preferred raw material is a preconcentrated sweet whey from cheesemaking, preferably at 10-23% by weight and decationized or completely deionized, that is to say freed of cation and freed of anion.

Another preferred material is a protein concentrate of lactose-free and cation-free sweet whey.

These raw materials may be provided in liquid form or in powdered form, and in the latter case, they are dispersed in water, preferably demineralized with a view to their subsequent treatment.

These raw materials can be derived from the milk of ruminants, such as cows, goats, sheep or buffaloes.

According to a first embodiment of the process, the liquid raw material is brought into contact with a weakly anionic resin in a reactor, with gentle stirring, at a temperature < 50°C, preferably between 0 and 15°C. The stirring should be just sufficient for fluidization of the resin bed. It can be produced, for example, by a stirrer or, preferably, by the introduction of a stream of fluid, for example of air or nitrogen under pressure through the bottom of the reactor.

It is possible to use any anion-exchange resin whose matrix is hydrophobic and in which the exchanging groups are weakly basic in macroporous or macrocross-linked, preferably polystyrene or polyacrylic, gel form, particularly based on polystyrene/divinylbenzene copolymer and preferably macrocross-linked because of considerations of resistance to osmotic shocks. The active groups are generally primary to tertiary amines. Such a resin should predominantly be in alkaline form (termed hereinafter OH^- form) and therefore its active sites should preferably have been largely regenerated in this form.

During this bringing into contact, the active sites of the resin are exchanged against the GMP molecules, producing a gradual increase in the pH of the treated liquid, up to a stabilized final value, for example of 4.5 to 5.5 depending on the raw material used. The duration of the operation and the respective quantities

of resin and of treated liquid are chosen as a function of the composition of the starting material and the desired quantity of GMP. This operation lasts from 1 to 10 h, for example for about 4 h. The respective proportions of resin and of liquid to be treated can vary widely and are, by volume, from 1:1 to 1:30 and preferably from 1:1 to 1:10, depending on the desired degree of separation of the GMP.

According to another embodiment, the liquid can be percolated through a column filled with the resin, the treated liquid collected therefrom and the GMP adsorbed onto the resin recovered by elution. To do this, the procedure can be carried out continuously or semicontinuously, for example by extracting the saturated resin from the column countercurrentwise and by replacing it with freshly regenerated resin.

The preceding embodiments, in a reactor and in a column, can be combined, for example, using a mixed device whose upper part is a reactor provided with means for stirring or for production of a fluidized bed containing the resin, separated by a grid or a filter from a lower part consisting of a column where, at the end of the treatment, the resin can be recovered, for example by decantation, and the treated liquid drawn off.

The liquid thus treated can be concentrated, for example by evaporation, and then dried, for example by spray-drying in a drying tower.

The powder thus obtained advantageously serves as protein raw material in the preparation of infant products and is remarkable because of its desired amino acid profile, its aminogram showing a reduction in threonine and an enrichment in aromatic amino acids such as tryptophan.

To separate the GMP therefrom, the resin is first treated by washing, for example with demineralized water, and then, where appropriate, with a dilute saline solution or a dilute acidic solution and it is rinsed with demineralized water. The actual desorption of the GMP is carried out with an aqueous solution of acid, base or salt, preferably with a basic aqueous solution, for example NaOH, KOH or $Ca(OH)_2$, advantageously of concentration < 8% by weight, preferably of 0.5 to 3%, followed by washing with demineralized water. In this manner, the resin is regenerated at the same time. The eluate and the washings are then combined and they are then demineralized, for example by ultrafiltration or nano-filtration on a membrane with a mean cut-off region of about 3000 daltons and the retentate is dried, for example by freeze-drying.

The GMP thus obtained is substantially free of fat and of lactose and is low in whey proteins.

It preferably contains, by weight:
< 1% fat,
< 0.2% of lactose, and
< 3% of true whey proteins.

The GMP can be used in its known applications, for example for its biological properties in oral, parenteral or subcutaneous pharmaceutical compositions as antithrombotic, antidiarrhoeal or antibacterial agent or preferably as agent against plaque and against caries in compositions for dental hygiene, or alternatively in foods, for example confectionery products for its properties against plaque and against caries, for its functional properties as emulsifying, gelling or foaming agent or for its dietetic properties, for example in antiphenylketonuria infant compositions because it does not contain phenylalanine.

A significant advantage of the process according to the invention is that there is no decrease in the performance of the resin or fouling thereof, even after up to 150 treatment cycles.

The examples below illustrate the invention, as well as Figure 1 of the drawing, showing, schematically and with no limitation being implied, a preferred device for carrying out the invention. In the examples, the parts and percentages are by weight unless otherwise stated.

Example 1

For the treatment, reactor 1 is used which consists, in its upper part, of a principal tank 2 communicating in its lower part with a compartment 3 with a smaller diameter than that of the tank 2. The tank 2 is provided with a rinsing liquid inlet channel 4, an inlet for gas under pressure 5, a safety valve 6 allowing the gas pressure in the reactor 1 to be regulated. At a level close to its base, the tank 2 is provided with a strainer 7 and a channel for drawing off liquid 8.

At the level of the compartment 3, the reactor is provided with a pH-meter 9, a gas inlet 10 and communicates by a three-way valve 11 with an inlet channel 12 for liquid to be treated and a discharge channel 13 for the treated liquid. At the base of the compartment 3, there is provided a grid or a perforated plate 14 whose role is to collect the resin beads 15. Under the grid 14, a drawing-off channel 16 brings the liquid via the pump 17 to the buffer tank 18 provided with a level controlling device 19 and from there to the channel 20 via the pump 21. The channel 20 is connected either to the channel 12, or to the discharge overflow 22.

A bovine sweet whey protein concentrate, conventionally treated by electrodialysis and freed of cation on a strong cationic resin, is dispersed in deionized water such that the solution has a dry matter content of 6.5%.

The concentrate has the composition below:

	%
Proteins (GMP included)	76
Lactose	4.8
Ash	2.5
Lipids	8
Water	balance for 100

127 kg of the dispersion, of initial pH 4.25, at the temperature of 12°C, are transferred via the channel 12 into the reactor 1 through whose base air is introduced by bubbling at the level of the compartment 3, by the inlet 10 via a non-return valve 23, so as to create a fluidized bed of resin beads 15 comprising 23 kg of weak anionic resin of hydrophobic matrix based on polystyrene (IMAC HP 661®, Rohm & Haas, regenerated in OH^- form). The resin beads 15 are stirred for 4 h in contact with the dispersion due to the turbulence created by the fluidization. The pH is constantly controlled by means of the pH-meter 9. Stabilization of the pH at 5.08 indicates the end of the reaction. The air supply at 10 is then cut off and air is introduced through the top of the reactor in 5 above the liquid level 24, which has the effect of pushing the liquid and of settling out the resin beads in the lower part 3 of the reactor 2 where they are retained by the grid 14. The treated liquid is drawn off by gravity through the channel 8 and through the channel 16 by means of the pump 17 towards the buffer tank 18 and it is discharged by the channel 20 by means of the pump 21 and beyond towards the outlet by the channels 12 and 13.

After concentration of the liquid to 28% dry matter by evaporation, the concentrate is spray-dried in a drying tower (these operations not being represented).

Analysis of the concentrate by high-performance liquid chromatography (HPLC) shows that the reaction removed 91% of the starting GMP. Moreover, the powder contains 95% of the starting whey proteins.

To recover the GMP, the reactor and the resin are washed with deionized water starting with the channel 25 and the valve 26, then the channel 4 through the reactor up to the outlet via channels 12 and 13. The GMP is eluted through the same circuit with twice 40 l of aqueous solution at 2% NaOH distributed by the channel 27 and the valve 28 and rinsing is carried out with 30 l of deionized water. After having combined the eluate and rinsing volumes, the whole is concentrated to a volume of 25 l by ultrafiltration or nano-filtration with a membrane having a nominal cut-off of 3000 daltons, and then the retentate is freeze-dried (these operations not being represented) and 750 g of GMP are obtained, corresponding to a yield of 82% relative to the starting GMP.

Periodically, the resin is subjected to acidic regeneration after alkaline regeneration once the equivalent of 10 volumes of resin bed has been treated. To do this, after elution of the GMP with the alkaline solution as described above, a concentrated aqueous solution of HCl is supplied by the channel 29 and the valve 30, respectively 25 for the water. The resin is then converted to the OH^- form by passing a concentrated aqueous solution of NaOH from the channels 27, respectively 25 for the water, then 4, and then leaves the reactor 1 by the channel 16, is taken up by the pump 17 to the buffer tank 18, and then by the pump 21 and discharged by the channel 20 and the overflow 22

to the effluent treatment. Following this operation, the resin is ready for another treatment cycle.

Example 2

A bovine sweet whey is used which has been previously concentrated to 17% dry matter, and then demineralized by electrodialysis, freed of cation on a strong cationic resin column, freed of anion on a weak anionic resin column and spray-dried in a drying tower, of the composition indicated below:

	%
Proteins (GMP included)	11.7
Lactose	81.7
Ash	1
Lipids	1
Water	balance for 100

This demineralized whey powder is solubilized in deionized water. After cation removal the solution has an initial pH of 3.8. In the preceding plant, 392 kg of this solution are treated at the temperature of 8°C, while stirring it in the reactor in the presence of 23 kg of weak anionic resin of hydrophobic matrix based on polystyrene (IMAC HP 661®, Rohm & Haas, regenerated in OH^- form) for 4 h. Stabilization of the pH at 4.89 indicates the end of the reaction. The liquid is then drawn off and the resin is recovered as above.

After concentration of the liquid to 45% dry matter by evaporation, the concentrate is spray-dried in a drying tower.

Analysis of the concentrate by HPLC shows that the reaction has removed 89% of the starting GMP. Moreover, the powder contains 9.1% of whey proteins, which corresponds to a yield of 90% of the whey proteins.

To recover the GMP, the resin is washed successively with deionized water, with 30 l of an aqueous solution at 0.5% HCl and with 30 l of deionized water, and then the GMP is eluted with twice 40 l of aqueous solution at 2% $Ca(OH)_2$ and the rinsing is carried out with 30 l of deionized water. After having combined the eluate and rinsing volumes, the whole is concentrated to a volume of 25 l by ultrafiltration with a membrane having a nominal cut-off of 3000 daltons, and then the retentate is freeze-dried and 900 g of GMP are obtained, corresponding to a yield of 80% relative to the starting GMP.

Example 3

A sweet whey, preconcentrated to 18% dry matter, freed of cation by treatment on a column of strong cationic resin, whose initial pH is 1.09, is used as starting material.

In the preceding plant, 70 kg of this whey are treated at the temperature of 25°C while stirring it in the reactor in the presence of 14 kg of weak anionic resin of hydrophobic matrix based on polystyrene (IRA 96®, Rohm & Haas, regenerated in OH^- form) for 4 h. The stirring is provided by the creation of a fluidized bed of resin beads with bubbling of nitrogen. Stabilization of the pH at 4.79 indicates the end of the reaction. The liquid is then separated from the resin as above. After concentration of the liquid to 45% dry matter by evaporation, the concentrate is spray-dried in a drying tower.

Analysis of the powder by HPLC shows that the reaction removed 85% of the starting GMP. However, the powder contains 9.2% of the whey proteins, corresponding to a yield of 90% of the whey proteins.

Analysis of the aminogram of the concentrate shows a profile which is characterized by a 28% decrease in threonine, by an 18% increase in arginine and by a 20% increase in tryptophan.

To recover the GMP, the resin is successively washed with deionized water, with 50 l of an aqueous solution at 0.05% NaCl and twice 50 l of deionized water, and then the GMP is eluted with twice 25 l of aqueous solution at 0.6% KOH and rinsing is carried out with 10 l of deionized water. After having combined the eluate and rinsing volumes, the whole is concentrated to a volume of 25 l by ultrafiltration with a membrane having a nominal cut-off of 3000 daltons, and then the retentate is freeze-dried, and 175 g of GMP are obtained, corresponding to a yield of 80% relative to the starting GMP.

Example 4

A powder of sweet whey ultrafiltration permeate, freed of most of its salts, whose composition is the following, is used as starting material:

	%
Proteins (GMP included)	2.75
Lactose	> 90
Ash	1.5
Water	balance for 100

The preceding powder is dissolved in demineralized water such that the solution has a dry matter content of 19.35%. This solution is freed of cation by passage over a column of strong cationic resin IR 120® Rohm & Haas), which leads to a solution containing 18.73% of dry matter whose pH is 2.77.

565 g of this solution and 56.5 g of weak anionic resin of hydrophobic matrix based on polystyrene (IMAC

HP 661®, Rohm & Haas, regenerated in OH^- form) are stirred for 3 h at 10°C until the pH is stabilized at a final value of 4.53. The permeate thus treated is then separated from the resin beads by filtration and it is freeze-dried.

The whey protein permeate thus treated contains 1.75% of proteins. Analysis of its aminogram shows a profile characterized by a 20% decrease in threonine and by a 50% increase in tryptophan.

To recover the GMP, the resin is washed with 1 l of deionized water, and then the GMP is eluted with 50 ml of aqueous solution at 0.6% NaOH, and then rinsing is carried out with 20 ml of deionized water. After having combined the eluate and rinsing volumes, the whole is concentrated by ultrafiltration with a membrane having a nominal cut-off of 3000 daltons, and then the retentate is freeze-dried and 870 mg of GMP are obtained.

Example 5

3.5 l of sweet whey, preconcentrated to 20% dry matter, freed of cation on a column of strong cationic resin and of pH 1.09, are percolated through a column containing 450 ml of weak anionic resin of hydrophobic matrix based on polystyrene (IMAC HP 661®, Rohm & Haas), at the rate of 2 bed volumes/h.

The equivalent of 4 bed volumes are recovered, constituting 4 equal fractions of pH ranging from 6 to 3 and in which the quantity of GMP removed ranges from 50 to 9% (evaluated by HPLC). After combining the 4 fractions, a solution of pH 4.5 is obtained in which 25% of the GMP has been removed (compared with the starting whey material).

To recover the GMP, the procedure is carried out as in Example 1 and equivalent results are obtained as regards the purity of the GMP.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. Process for the ion-exchange treatment of a liquid lactic raw material containing GMP, with the aim of recovering, on the one hand, a product which can be used as protein source and, on the other hand, GMP in purified form, comprising the following steps:

i) decationization of the liquid raw material, such that the pH has a value of 1 to 4.5,

ii) bringing the said liquid into contact with a weak anionic resin of hydrophobic matrix, predominantly in alkaline form up to a stabilized pH,

iii) separation of the resin and the liquid product which is recovered, and

iv) desorption of GMP from the resin.

2. Process according to Claim 1, wherein the raw material is a preconcentrated sweet whey from cheesemaking.

3. Process according to Claim 2, wherein the preconcentrated sweet whey from cheesemaking is at 10-23% by weight.

4. Process according to Claim 2, wherein the preconcentrated sweet whey is freed of cations.

5. Process according to Claim 2, wherein the preconcentrated sweet whey is completely deionized.

6. Process according to Claim 1, wherein the raw material is a protein concentrate of lactose-free and cation-free sweet whey.

7. Process according to Claim 1, wherein the raw material is

- the product of hydrolysis, by a protease, of a native casein obtained by acid precipitation of skimmed milk with an inorganic acid or by biological acidification, where appropriate with addition of calcium ions,

- the product of hydrolysis by a protease, of micellar casein, obtained for example by microfiltration of a skimmed milk, or alternatively,

- the product of hydrolysis of a caseinate by a protease.

8. Process according to Claim 1, wherein the raw material is a permeate of the ultrafiltration of sweet whey.

9. Process according to Claim 1, wherein the liquid raw material is brought into contact with a weak anionic resin predominantly in alkaline form in a gently stirred

reactor at a temperature of less than 50°C to produce a gradual increase in the pH of the treated liquid, until stabilization is obtained, and then the liquid is separated from the resin by filtration or centrification.

10. Process according to Claim 9 wherein the gently stirred reactor is at a temperature between 0 and 15°C.

11. Process according to Claim 9 or 10, wherein the liquid raw material is in contact with the weak anionic resin in the gently stirred reactor for between one and several hours.

12. Process according to Claim 9, 10 or 11, wherein any weakly basic anion-exchange resin in macroporous or macrocross-linked gel form, whose matrix is hydrophobic, is used.

13. Process according to Claim 9, 10 or 11, wherein the liquid thus treated is concentrated and then dried.

14. Process according to Claim 13, wherein the liquid is concentrated by evaporation.

15. Process according to Claim 13 or 14, wherein the concentrated liquid is dried by spray drying in a drying tower.

16. Process according to Claim 1, wherein to separate the GMP therefrom in purified form, the resin is first treated by washing, the GMP is then desorbed with an acidic, basic or saline aqueous solution, rinsed with demineralized water, the eluate and the rinsings being combined and demineralized, the retentate being dried.

17. Process according to Claim 16, wherein the GMP is desorbed with an aqueous solution of NaOH, KOH or $Ca(OH)_2$.

18. Process as claimed in Claim 16 or 17, wherein the aqueous solution of NaOH, KOH or $Ca(OH)_2$ is at a concentration of less than 8%.

19. Process as claimed in Claim 16, 17 or 18, wherein the eluate and rinsings are demineralized by ultrafiltration or nanofiltration on a membrane with a mean cut-off region of about 3000 daltons.

20. Process as claimed in any one of Claims 16 to 19 wherein the retentate is dried by freeze drying.

21. Use of the purified GMP which can be obtained by the process according to any one of claims 16 to 20, for preparing an antidiarrhoeal or antibacterial pharmaceutical composition.

22. Use of the purified GMP which can be obtained by the process according to any one of claims 16 to 20, for preparing a dental hygiene composition against plaque and against caries.

23. Process for the ion-exchange treatment of a liquid lactic raw material containing GMP substantially as hereinbefore described with reference to any one of the embodiments of the invention illustrated in the accompanying drawings and/or examples.

24. Use of the purified GMP which can be obtained by the process for the ion-exchange treatment of a liquid lactic raw material containing GMP substantially as hereinbefore described with reference to any one of the embodiments of the invention illustrated in the accompanying drawings and/or examples.

DATED this 10th Day of January 2002

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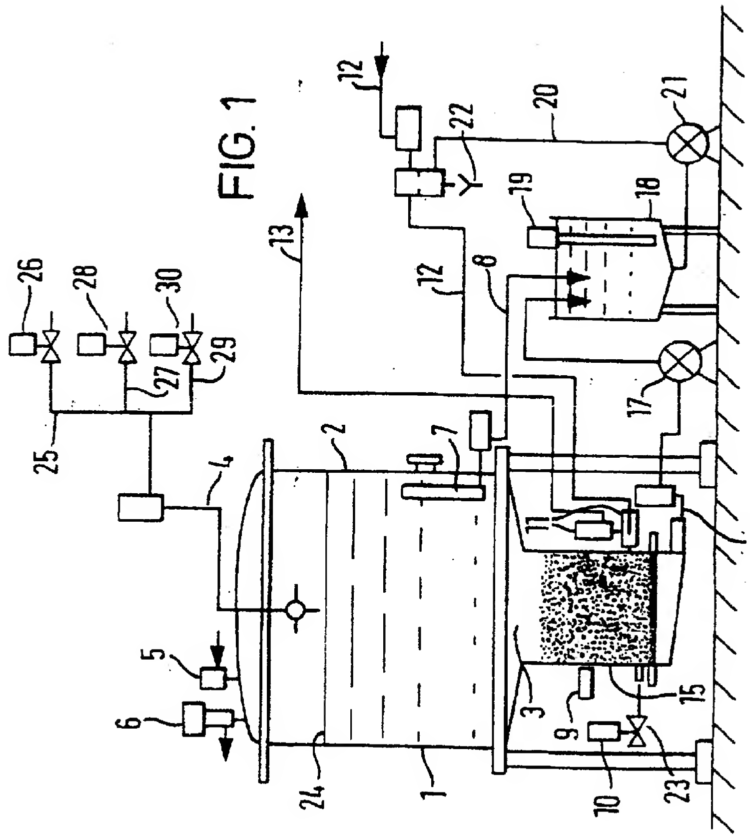

FIG. 1